Review Article

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The Korean Heart Rhythm Society's 2014 Statement on Antithrombotic Therapy for Patients with Nonvalvular Atrial Fibrillation: Korean Heart Rhythm Society

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In patients with nonvalvular atrial fibrillation (AF), the risk of stroke varies considerably according to individual clinical status. The CHA_2DS_2-VASc score is better than the $CHADS_2$ score for identifying truly lower risk patients with AF. With the advent of novel oral anticoagulants (NOACs), the strategy for antithrombotic therapy has undergone significant changes due to its superior efficacy, safety and convenience compared with warfarin. Furthermore, new aspects of antithrombotic therapy and risk assessment of stroke have been revealed: the efficacy of stroke prevention with aspirin is weak, while the risk of major bleeding is not significantly different from that of oral anticoagulant (OAC) therapy, especially in the elderly. Reflecting these pivotal aspects, previous guidelines have been updated in recent years by overseas societies and associations. The Korean Heart Rhythm Society has summarized the new evidence and updated recommendations for stroke prevention of patients with nonvalvular AF. First of all, antithrombotic therapy must be considered carefully and incorporate the clinical characteristics and circumstances of each individual patient, especially with regards to balancing the benefits of stroke prevention with the risk of bleeding, recommending the CHA_2DS_2-VASc score rather than the $CHADS_2$ score for assessing the risk of stroke, and employing the HAS-BLED score to validate bleeding risk. In patients with truly low risk (lone AF, CHA_2DS_2-VASc score of 0), no antithrombotic therapy is recommended, whereas OAC therapy, including warfarin (international normalized ratio 2–3) or NOACs, is recommended for patients with a CHA_2DS_2-VASc score ≥ 2 unless contraindicated. In patients with a CHA_2DS_2-VASc score of 1, OAC therapy should be preferentially considered, but depending on bleeding risk or patient preferences, antiplatelet therapy or no therapy could be permitted. **(Korean Circ J 2015;45(1):9–19)**

KEY WORDS: Atrial fibrillation; Antithrombotic agent; Anticoagulant.

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Introduction

The prevalence of atrial fibrillation (AF) is approximately 1.5–2% of the general population in the developed world, with a tendency to increase abruptly with age, and is estimated to be about 10% of the population over 80 years old. AF is accompanied by a five-fold risk of stroke and a three-fold incidence of congestive heart failure, as well as higher mortality.[1] Especially in patients with AF, stroke has a tendency to involve a larger territory, with brain infarction that results in more severe neurological disability than that by other causes. Hence, the importance of antithrombotic therapy on AF has been consistently emphasized.[2]

Since 2003, pivotal results from randomized controlled trials have been sequentially released that detail the efficacy and safety of novel oral anticoagulants (NOACs) for the prevention of stroke in nonvalvular AF patients. Compared with conventional antithrombotics such as aspirin, clopidogrel or warfarin, NOACs have different action mechanisms that are classified into two classes: oral direct thrombin inhibitor (ximelagatran, dabigatran) and oral direct factor Xa inhibitor (rivaroxaban, apixaban, edoxaban).[3-8] While ximelagatran was developed first and withdrawn in the middle of a clinical application due to severe liver toxicity, other NOACs developed afterward have had favorable risk-benefit profiles with non-inferior or superior reductions in stroke, intracranial hemorrhage (ICH), and mortality, and with similar incidence of major bleeding as warfarin. Due to these findings, NOACs have been recommended as anticoagulant therapy for nonvalvular AF patients in the updated guidelines of Asian and Western societies since 2010.

The authors have reviewed guidelines issued in recent years by Asian, European, and North American societies and organizations, and based on these guidelines, provide updated recommendations for the prevention of stroke in nonvavular AF patients.

Previous Recommendations for Antithrombotic Therapies in Korea

In Korea, the clinical guideline for the prevention of stroke in patients with AF was published in 2009, even before the introduction of NOACs in clinical practice. The summary of antithrombotic therapies for the prevention of stroke in nonvalvular AF patients was as follows:[9]

1) Antithrombotic therapy (warfarin or aspirin) was recommended to prevent stroke in patients with nonvalvular AF according to assessment of their absolute stroke risk, estimated bleeding risk, patient preferences, and access to high-quality anticoagulation monitoring.

2) Warfarin {international normalized ratio (INR) 2.0 to 3.0} was recommended for high-risk (4% annual risk of stroke) patients (and most moderate-risk patients according to an assessment of bleeding risk) with AF who had no clinically significant contraindications to oral anticoagulants (OACs).

3) Although not yet established by randomized studies, in patients over 75 years of age, warfarin (INR 2.0 to 3.0) may be used for the primary prevention of stroke in patients with AF.

Thereafter, due to the excellent anticoagulant efficacy of NOACs for nonvalvular AF patients and the revision of overseas recommendations, an update was issued in 2012 on the primary prevention of stroke in AF patients by the Korean Stroke Society.[2]

However, in real clinical practice, aspirin is preferred for patients with low-risk of stroke, and overused for nonvavular AF patients without risk factors (lone AF, CHA_2DS_2-VASc score of 0) that obviously gain no benefit from antithrombotic therapy. On the other hand, despite the superior efficacy in stroke prevention compare to antiplatelets such as aspirin or clopidogrel, anticoagulation with warfarin (oral vitamin K antagonist) is inadequately underused because of low compliance owing to frequent INR tests, concern about severe bleeding complications, and INR fluctuations due to interaction with concomitant medications, food, or herbal medicine.

Recently Updated Overseas Recommendation and Evidences

Stroke and bleeding risk assessment with antithrombotic therapy in nonvalvular atrial fibrillation patients

The $CHADS_2$ score, expressed as an acronym, has been widely used to evaluate the risk of stroke in AF patients and assigns a single point for several factors, namely, Congestive Heart Failure, Hypertension, Age (over 75 years old) and Diabetes Mellitus, and two points for Stroke or transient ischemic attack (TIA). However, it has been found to have a limitation with discriminating "ruly low-risk" patients from low-risk ($CHADS_2$ score=0) patients that have no need for antithrombotic therapy. To overcome this issue, the European Society of Cardiology (ESC) 2010 guideline introduced the CHA_2DS_2-VASc score, which incorporates additional weights for age (2 points for age over 75 year old, 1 point for 65–74), gender (1 point for female) and vascular disease (1 point) (Table 1).[10] Thereafter, the Canadian Cardiovascular Society (CCS) AF 2012 guideline, APHRS 2013 guideline, and American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Rhythm Society (HRS) 2014 guideline were revised to prefer the CHA_2DS_2-VASc score for evaluating the risk of stroke or to adopt CHA_2DS_2-VASc score instead of the $CHADS_2$ score.[11-13] However, antithrombotic therapy is not recommended for female patients with no other risk factors of stroke.

In previous recommendations, a $CHADS_2$ score of 1 was the decisive

Table 1. The CHA_2DS_2-VASc score

Letter	Risk factor	Score
C	Congestive heart failure/LV dysfunction	1
H	Hypertension	1
A_2	Age ≥75	2
D	Diabetes mellitus	1
S_2	Stroke/TIA/thrombo-embolism	2
V	Vascular disease*	1
A	Age 65–74	1
S	Sex category (i.e., female sex)	1
	Maximum score	9

Congestive heart failure/LV dysfunction means LV ejection fraction ≤40%. Hypertension includes the patients with current antihypertensive medication. *Prior myocardial infarction, peripheral artery disease, aortic plaque. LV: left ventricular, TIA: transient ischemic attack

Table 2. The HAS-BLED bleeding risk score

Letter	Risk factor	Score
H	Hypertension	1
A	Abnormal renal and liver function (1 points each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g., age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
	Maximum score	9

Hypertension means systolic blood pressure >160 mm Hg. Abnormal renal function means the presence of chronic dialysis or renal transplantation or serum creatinine ≥200 μmol/L (about 2.262 mg/dL: 88.4 μmol/L=1.0 mg/dL). Abnormal liver function means chronic hepatic disease or biochemical evidence of significant liver dysfunction (e.g., bilirubin >two times of upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase >three times of upper limit normal, etc.). Bleeding means previous bleeding history and/or predisposition to bleeding, e.g., bleeding diathesis, anemia, etc. Labile INRs means unstable/high INRs or poor time in therapeutic range (e.g., <60%). Drugs/alcohol use means concomitant use of drugs, such as antiplatelet agents, nonsteroidal anti-inflammatory drugs, or alcohol abuse, etc. INR: international normalized ratio

factor for implementing antithrombotic therapy. Accumulating evidence suggest that the CHA_2DS_2-VASc score is better at identifying "truly low-risk" patients in AF, and is as good as or possibly better than the $CHADS_2$ score in predicting patients who will develop stroke and thromboembolism.[14] Hence the CHA_2DS_2-VASc score should be adopted in Korea to avoid unnecessary antithrombotic therapy among low-risk patients, and to more precisely refine the risk of stroke in AF patients.

Antithrombotic therapy for stroke prevention should be concerned with balancing the risk of stroke against the risk of major bleeding such as ICH, the most dangerous complication, and severe bleeding that require more than 2 pints of transfusion. Generally, the risk of bleeding is proportionally increased with antithrombotic intensity in the following order: 1) aspirin (75–325 mg/day) or clopidogrel (75 mg/day), 2) a combination of aspirin and clopidogrel, and 3) low dose dabigatran (110 mg bid.), 4) high dose dabigatran (150 mg bid.), rivaroxaban, apixaban and warfarin (INR: 2–3), which carry similar risks.[11]

The ESC 2010 and CCS AF 2012 guidelines recommended the use of HAS-BLED bleeding risk score for the evaluation of bleeding risk in clinical practice (Table 2). The HAS-BLED bleeding risk score considers the following as bleeding risk factors; Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INRs, Elderly (over 65 years old), and Drug/alcohol. According to this score system, the risk of major bleeding with a HAS-BLED score of 0–1 is about 1%, and about 12.5% annually with a HAS-BLED score of 5.[15] In patients with a HAS-BLED score of 3, the risk of major bleeding is about 3.74% and coincides with a high-risk of stroke in AF patients. Therefore, to minimize bleeding complications, vigilant caution and regular review are essential, as well as efforts to correct potentially reversible risk factors for bleeding in patients with HAS-BLED score ≥3. A high HAS-BLED score per se should not exclude patients from OAC therapy. NOACs can be recommended for patients with labile INRs because of its predictable effect without INR monitoring, and fewer food and drug interactions. Hypertension, previous stroke, TIA and old age, which are known as risk factors for stroke, overlap with the risk factors for concomitant bleeding. In daily clinical practice, caution should be taken because bleeding risk is often enhanced proportionally with increases in the CHA_2DS_2-VASc score.

Pivotal clinical trials using novel oral anticoagulants

Dabigatran versus Warfarin: The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY)[4]

The RE-LY clinical trial was a prospective, randomized, open-label, phase III trial comparing two blinded doses of dabigatran etexilte {110 mg bid (D110) or 150 mg bid (D150)} with adjusted-dose warfarin (INR 2.0–3.0), in which the primary outcome was stroke or systemic embolism. Primary outcome rates were 1.69% per year in the warfarin group, as compared with 1.53% per year in the D110 group {relative risk (RR), 0.91; 95% CI, 0.74 to 1.11; p<0.001 for noninferiority} and 1.11% per year in the D150 group {RR, 0.66; 95% confidence interval (CI), 0.53 to 0.82; p<0.001 for superiority}. The rate of major bleeding was 3.36% per year in the warfarin group, as compared with 2.71% per year in the D110 group (p=0.003) and 3.11% per year in the D150 group (p=0.31). The rate of hemorrhagic stroke was 0.38% per year in the warfarin group, as compared with 0.12% per year with the D110 group (p<0.001) and 0.10% per year

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with the D150 group (p<0.001). The mortality rate was 4.13% per year in the warfarin group, as compared with 3.75% per year with the D110 group (p=0.13) and 3.64% per year with the D150 group (p=0.051). Rates of hemorrhagic stroke and ICH were lower with both doses of dabigatran, but gastrointestinal bleeding was significantly higher in the D150 group.

In patients with AF, D110 was associated with rates of stroke and systemic embolism similar to those associated with warfarin, as well as lower rates of major hemorrhage. D150, as compared with warfarin, was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage.

Rivaroxaban versus Warfarin: Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for the Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF)[5]

The ROCKET AF clinical trial was a randomized, double-blind and double-dummy trial for either rivaroxaban 20 mg taken daily (15 mg daily for those with estimated creatinine clearance 30–49 mL/min) or dose-adjusted warfarin for patients with nonvalvular AF who were at considerably higher risk of stroke than those in other NOAC AF trials. The mean time in the therapeutic range (TTR) was 55%, which was lower than in other randomized trials. The primary end point, stroke or systemic embolism, occurred in 188 patients in the rivaroxaban group (1.7% per year) and in 241 in the warfarin group (2.2% per year) {hazard ratio (HR), 0.79; 95% CI, 0.66 to 0.96; p<0.001 for noninferiority}. In the intention-to-treat analysis, the primary end point occurred in 269 patients in the rivaroxaban group (2.1% per year) and in 306 patients in the warfarin group (2.4% per year) (HR, 0.88; 95% CI, 0.74 to 1.03; p<0.001 for noninferiority; p=0.12 for superiority). Major and nonmajor clinically relevant bleeding occurred in 1475 patients in the rivaroxaban group (14.9% per year) and in 1449 in the warfarin group (14.5% per year) (HR, 1.03; 95% CI, 0.96 to 1.11; p=0.44), with significantly lower ICH (0.5% vs. 0.7%, p=0.02) and fatal bleeding (0.2% vs. 0.5%, p=0.003) in the rivaroxaban group. However, GI bleeding was higher in the rivaroxaban group than in the warfarin group (3.3% vs. 2.2%, p<0.001).

In patients with AF, rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism. There was no significant difference between groups in the risk for major bleeding, although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group.

Apixaban versus Aspirin: Apixaban versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES)[6]

The AVERROES clinical trial was a randomized, double-blind and double-dummy trial with AF patients who were unsuitable candidates for warfarin, comparing the efficacy of apixaban to that of aspirin for the prevention of stroke or systemic embolism. There were 51 primary outcome events (1.6% per year) in the apixaban group and 113 (3.7% per year) in the aspirin group (HR, 0.45; 95% CI, 0.32 to 0.62; p<0.001). The mortality was 3.5% per year in the apixaban group and 4.4% per year in the aspirin group (HR, 0.79; 95% CI, 0.62 to 1.02; p=0.07). There were 44 cases of major bleeding (1.4% per year) in the apixaban group and 39 (1.2% per year) in the aspirin group (HR, 1.13; 95% CI, 0.74 to 1.75; p=0.57). Intracranial bleeding occurred in 11 cases with apixaban and 13 with aspirin. Apixaban reduced the risk of a first hospitalization for cardiovascular causes compared with aspirin (12.6% per year vs. 15.9% per year, p<0.001).

In patients with AF for whom vitamin K antagonist therapy was unsuitable, apixaban reduced the risk of stroke or systemic embolism without significantly increasing the risk of major bleeding or ICH.

Apixaban versus Warfarin: Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE)[7]

The ARISTOTLE clinical trial was a randomized, double-blind, double-dummy, phase III trial comparing apixaban (5 mg twice daily, or a dose adjustment to 2.5 mg twice daily in patients who met two of the following factors: ≥80 years, weight ≤60 kg or a serum creatinine ≥1.5 mg/dL) with dose-adjusted warfarin (INR 2.0–3.0) in patients with nonvalvular AF. The primary outcome was ischemic or hemorrhagic stroke or systemic embolism. The rate of primary outcome was 1.27% per year in the apixaban group, as compared with 1.60% per year in the warfarin group (HR, 0.79; 95% CI, 0.66 to 0.95; p<0.001 for noninferiority; p=0.01 for superiority). The rate of major bleeding was 2.13% per year in the apixaban group, as compared with 3.09% per year in the warfarin group (HR, 0.69; 95% CI, 0.60 to 0.80; p<0.001), and the mortality from any cause was 3.52% and 3.94%, respectively (HR, 0.89; 95% CI, 0.80 to 0.99; p=0.047). The rate of hemorrhagic stroke was 0.24% per year in the apixaban group, as compared with 0.47% per year in the warfarin group (HR, 0.51; 95% CI, 0.35 to 0.75; p<0.001), and the rate of ischemic or uncertain type of stroke was 0.97% per year in the apixaban group and 1.05% per year in the warfarin group (HR, 0.92; 95% CI, 0.74 to 1.13; p=0.42). In patients with AF, apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality.

Edoxaban versus Warfarin: The Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48)[8]

The ENGAGE AF-TIMI 48 clinical trial was a randomized, double-

blind, double-dummy trial comparing two once-daily regimens of edoxaban {high dose: 60 mg/day (E60), low dose: 30 mg/day (E30)} with warfarin. The primary end point was stroke or systemic embolism in patients with moderate to high risk AF. The annualized rate of the primary end point was 1.50% with warfarin, as compared with 1.18% with E60 (HR, 0.79; 97.5% CI, 0.63 to 0.99; p<0.001 for noninferiority) and 1.61% with E30 (HR, 1.07; 97.5% CI, 0.87 to 1.31; p=0.005 for noninferiority). In the intention-to-treat analysis, there was a trend favoring E60 versus warfarin (HR, 0.87; 97.5% CI, 0.73 to 1.04; p=0.08) and an unfavorable trend with E30 versus warfarin (HR, 1.13; 97.5% CI, 0.96 to 1.34; p=0.10). The rate of major bleeding was 3.43% per year with warfarin versus 2.75% per year with E60 (HR, 0.80; 95% CI, 0.71 to 0.91; p<0.001) and 1.61% with E30 (HR, 0.47; 95% CI, 0.41 to 0.55; p<0.001). The corresponding annual mortality from cardiovascular causes were 3.17% versus 2.74% (warfarin vs. E30; HR, 0.86; 95% CI, 0.77 to 0.97; p=0.01), and 2.71% (warfarin vs. E60; HR, 0.85; 95% CI, 0.76 to 0.96; p=0.008). The corresponding rates of the key secondary end point (a composite of stroke, systemic embolism, or death from cardiovascular causes) were 4.43% versus 3.85% (warfarin vs. E30; HR, 0.87; 95% CI, 0.78 to 0.96; p=0.005), and 4.23% (warfarin vs. E60; HR, 0.95; 95% CI, 0.86 to 1.05; p=0.32).

Both once-daily regimens of edoxaban were noninferior to warfarin with respect to the prevention of stroke or systemic embolism, and were associated with significantly lower rates of bleeding and death from cardiovascular causes.

The summary of clinical trials with NOACs is as follows: in the prevention of stroke, NOACs are superior or noninferior to warfarin therapy with well controlled INR, and show similar or lower incidence of bleeding complications.[16] Therefore NOACs can be recommended for patients with uncontrolled labile INRs, history of bleeding complications or previous stroke for whom warfarin was previously prescribed for prevention.[17]

Antiplatelet therapy in atrial fibrillation patients unsuitable for oral vitamin K antagonist therapy

Effect of Clopidogrel Added to Aspirin in Patients with Atrial Fibrillation: The Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE A)[18]

The ACTIVE A clinical trial compared the efficacy of aspirin monotherapy (75–100 mg/day) to that of combination therapy involving aspirin and clopidogrel (75 mg/day) in AF patients unsuitable for warfarin therapy with more than one risk factor for stroke. The primary outcome was the composite of stroke, myocardial infarction, non-central nervous system systemic embolism, or death from vascular causes. Major vascular events occurred in 832 patients with combination therapy (6.8% per year) and in 924 patients with monotherapy (7.6% per year) (RR, 0.89; 95% CI, 0.81 to 0.98; p=0.01). The difference was primarily due to a reduction in the rate of stroke with combination therapy. Stroke occurred in 296 patients with combination therapy (2.4% per year) and 408 patients with monotherapy (3.3% per year) (RR, 0.72; 95% CI, 0.62 to 0.83; p<0.001). Myocardial infarction occurred in 90 patients with combination therapy (0.7% per year) and in 115 with monotherapy (0.9% per year) (RR, 0.78; 95% CI, 0.59 to 1.03; p=0.08). Major bleeding occurred in 251 patients with combination therapy (2.0% per year) and in 162 patients with monotherapy (1.3% per year) (RR, 1.57; 95% CI, 1.29 to 1.92; p<0.001).

In patients with AF for whom vitamin K antagonist therapy was unsuitable, the addition of clopidogrel to aspirin reduced the risk of major vascular events, especially stroke, and increased the risk of major hemorrhage.

Clopidogrel Plus Aspirin versus Oral Anticoagulation for Atrial Fibrillation in the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE W): a randomized controlled trial[19]

The ACTIVE W was a randomized, controlled, open-label trial comparing the efficacy of combination therapy (aspirin 75–100 mg/day and clopidogrel 75 mg/day) to that of oral vitamin K antagonist (warfarin) therapy. The study was terminated early because of clear evidence of the superiority of warfarin therapy. There were 165 primary events in patients on warfarin therapy (annual risk 3.93%) and 234 in those on combination therapy (annual risk 5.60%; RR 1.44; 95% CI, 1.18 to 1.76; p=0.0003).

Warfarin therapy was superior to the combination therapy for prevention of vascular events in patients with AF at high risk of stroke, especially in those already taking oral anticoagulation therapy.

In a meta-analysis of sixteen trials, adjusted-dose warfarin showed a remarkable reduction of stroke in AF patients by 62% whereas aspirin reduced the risk of stroke by 22%, although major extracranial bleeding was increased by warfarin therapy.[20] Compared with aspirin, warfarin significantly decreased the risk of all strokes, including ischemic strokes, and cardiovascular events for patients regardless of AF type.[21] While advanced age (>75 years) is considered a clear risk factor for both stroke and bleeding, anticoagulant therapy should be regarded as the first-line of therapy rather than aspirin.[22] However, in real clinical practice, antiplatelet agents are applied as alternatives when OAC therapy is unsuitable. Based on the results of the ACTIVE A trial, even with cases where it is hard to decide whether aspirin monotherapy and combination therapy is more beneficial, combination therapy should be considered when the risk of bleeding is low.

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The Recommendation of Korean Heart Rhythm Society for Patients with Nonvalvular Atrial Fibrillation (Table 3)

1. Antithrombotic therapy selection should be considered using the same criteria, irrespective of the pattern of AF such as paroxysmal, persistent, and permanent.
2. The CHA_2DS_2-VASc score is recommended for the assessment of stroke risk.
   2-1. The CHA_2DS_2-VASc score should be used for appropriate antithrombotic therapy.
   2-2. NOACs or anticoagulant therapy using warfarin should be recommended for antithrombotic therapy when the CHA_2DS_2-VASc score is 1 or greater.
   2-3. Antithrombotic therapy is not recommended when the CHA_2 DS_2-VASc score is 0.
   2-4. The CHA_2DS_2-VASc score is considered as 0 when being female is the only risk factor.

In the ESC 2012 guideline, NOACs are preferably recommended over warfarin for patients with a score of 1 or greater, while no antithrombotic therapy is recommended for patients with a score of 0. In the APHRS 2013 guideline, NOACs or warfarin are recommended impartially for patients with a score ≥2. NOACs (dabigatrin or apixaban, excluding rivaroxaban) are preferably recommended for patients with a score of 1, whereas rivaroxaban or warfarin are considered as alternatives. No antithrombotic therapy is recommended for patients with a score of 0. In the ROCKET AF clinical trial, rivaroxaban was administered to patients with $CHADS_2$ score of 2 or greater. Hence, it is recommended as an alternative when the CHA_2DS_2-VASc score is 1 (APHRS 2013). Meanwhile, in the 2014 AHA/ACC/HRS guideline, the strategy for antithrombotic therapy for patients with CHA_2DS_2-VASc score of 1 seems to be diverse: no antithrombotic therapy or treatment with OAC or aspirin can be considered.

3. Warfarin is recommended in the following cases:
   3-1. Patients with valve replacement or rheumatic valve disease.
   3-2. Patients with nonvalvular AF in whom INR is well controlled and no significant bleeding is present.
4. Optimal INR during warfarin treatment
   4-1. Optimal INR range is 2–3.
   4-2. Time in therapeutic range should be at least over 60% to maximize to the benefit of warfarin

In the APHRS 2013 guideline, the optimum range of INR is considered to be 1.6–2.6 in Asian elderly (≥70 years old) to minimize cerebral hemorrhage and other severe bleeding complications as well as to effectively prevent ischemic stroke.

5. Aspirin monotherapy or combination therapy with aspirin and clopidogrel can be considered when oral anticoagulation therapy is not suitable or patients refuse the use of OACs.
6. Oral anticoagulation therapy may be judiciously combined with antiplatelet therapy in the following cases:
   6-1. Recurrence of thromboembolism despite adequate oral anticoagulation therapy.
   6-2. Concomitant antiplatelet therapy may be considered for the treatment of nonembolic cerebral infarction or TIA.
   6-3. Presence of concomitant ischemic heart disease.
   6-4. Coronary artery stenting.
7. Switch from warfarin to NOACs, and cautions for the administration of NOACs.
   7-1. NOACs may not be used in place of warfarin in patients with stable anticoagulation control without bleeding complications.
   7-2. NOACs are recommended instead of warfarin for patients requiring anticoagulation therapy who have hypersensitivity or contraindication against warfarin, cannot maintain an INR within the optimal range, or have cerebral hemorrhage despite adequate INR maintainance.
   7-3. For the administration of dabigatran, 150 mg twice daily is recommended as a standard regimen. Dose reduction (110 mg twice daily) should be considered in the following cases:
   - Elderly patients (≥80 years old), concomitant administration of interacting drugs (e.g., verapamil), high bleeding risk (HAS-BLED score ≥3), or moderate renal dysfunction (CrCl 30–49 mL/min).
   7-4. For the administration of rivaroxaban, 20 mg once daily is recommended as a standard regimen. Dose reduction (15 mg once daily) should be considered in the following cases:
   - High bleeding risk (HAS-BLED score ≥3) or moderate renal dysfunction (CrCl 30–49 mL/min).
   7-5. For the administration of apixaban, 5 mg twice daily is recommended as a standard regimen. Dose reduction (2.5 mg twice daily) should be considered for the following cases:
   - Renal dysfunction (CrCl 30–49 mL/min)
   - Patients who have 2 or more of the following 3 factors: Elderly patients (≥80 years old), body weight ≤60 kg, or serum creatinine level ≥1.5 mg/dL.
   7-6. Assessment of renal function should be carried out prior to the use of NOACs and annually monitored in patients with normal (CrCl ≥80 mL/min) or mild renal dysfunction (CrCl 50–79 mL/min). It should be monitored 2–3 times per year in patients with moderate renal dysfunction (CrCl 30–49 mL/min).
   7-7. NOACs are not recommended for patients with severe

Table 3. The recommendation of the Korean Heart Rhythm Society for patients with nonvalvular AF

1. The selection of antithrombotic therapy should be considered using the same criteria irrespective of the pattern of AF such as paroxysmal, persistent, and permanent.
2. The CHA_2DS_2-VASc score is recommended for the assessment of stroke risk.
   2-1. The CHA_2DS_2-VASc score should be used for the appropriate antithrombotic therapy.
   2-2. NOACs or anticoagulant therapy using warfarin should be recommended for antithrombotic therapy when the CHA_2DS_2-VASc score is 1 or greater.
   2-3. Antithrombotic therapy is not recommended when the CHA_2DS_2-VASc score is 0.
   2-4. The CHA_2DS_2-VASc score is considered as 0 when being female is the only risk factor.
3. Warfarin is recommended in the following cases:
   3-1. Patients with valve replacement or rheumatic valve disease.
   3-2. Patients with nonvalvular AF in whom INR is well controlled and no significant bleeding is present.
4. Optimal INR during warfarin treatment
   4-1. Optimal INR range is 2–3.
   4-2. Time in therapeutic range should be at least over 60% to maximize the benefit of warfarin.
5. Aspirin monotherapy or combination therapy with aspirin and clopidogrel can be considered when oral anticoagulation therapy is not suitable or patients refuse the use of oral anticoagulants.
6. Oral anticoagulation therapy may be judiciously combined with antiplatelet therapy in the following cases:
   6-1. Recurrence of thromboembolism despite adequate oral anticoagulation therapy.
   6-2. Concomitant antiplatelet therapy may be considered for the treatment of nonembolic cerebral infarction or TIA.
   6-3. Presence of concomitant ischemic heart disease.
   6-4. Coronary artery stenting.
7. Switch from warfarin to NOACs, and cautions for the administration of NOACs.
   7-1. NOACs may not be used in place of warfarin in patients with stable anticoagulation control without bleeding complications.
   7-2. NOACs are recommended in place of warfarin for patients requiring anticoagulation therapy who have hypersensitivity or contraindication against warfarin, cannot maintain an INR within the optimal range, or have cerebral hemorrhage despite an INR that is adequately maintained.
   7-3. For the administration of dabigatran, 150 mg twice daily is recommended as a standard regimen. Dose reduction (110 mg twice daily) should be considered in the following cases:
   - Elderly patients (≥80 years old), concomitant administration of interacting drugs (e.g., verapamil), high bleeding risk (HAS-BLED score ≥3), or moderate renal dysfunction (CrCl 30–49 mL/min).
   7-4. For the administration of rivaroxaban, 20 mg once daily is recommended as a standard regimen. Dose reduction (15 mg once daily) should be considered in the following cases:
   - High bleeding risk (HAS-BLED score ≥3) or moderate renal dysfunction (CrCl 30–49 mL/min).
   7-5. For the administration of apixaban, 5 mg twice daily is recommended as a standard regimen. Dose reduction (2.5 mg twice daily) should be considered for the following cases:
   - Renal dysfunction (CrCl 30–49 mL/min)
   - Patients who have 2 or more of the following 3 factors:
   Elderly patients (≥80 years old), body weight ≤60 kg, or serum creatinine level ≥1.5 mg/dL.
   7-6. The assessment of renal function should be carried out prior to the use of NOACs and annually monitored in patients with normal (CrCl ≥80 mL/min) or mild renal dysfunction (CrCl 50–79 mL/min). It should be monitored 2–3 times per year in patients with moderate renal dysfunction (CrCl 30–49 mL/min).
   7-7. NOACs are not recommended in patients with severe renal dysfunction (CrCl <30 mL/min).
8. Anticoagulant therapy for patients who are scheduled for an invasive procedure or a surgery with the possibility of bleeding complications.
   8-1. For patients with warfarin therapy, INR should be measured within 24 hours before an invasive procedure or a surgery, and an INR of ≤1.5 is generally considered safe with regard to the risk of periprocedural or perioperative bleeding. Warfarin can be reintroduced 24 hours later when hemostasis is confirmed and the patient is under a stable condition.
   8-2. For patients with CrCl ≥50 mL/min, dabigatran should be ceased 1 day prior to procedures with low bleeding risk, and 2–3 days for high bleeding risk procedures. For patients with CrCl 30–49 mL/min, dabigatran should be ceased 2 days prior to procedures with low bleeding risk, and 3–4 days prior to procedures with high bleeding risk.
   8-3. For patients with CrCl ≥30 mL/min, rivaroxaban should be ceased 1 day prior to procedures with low bleeding risk, and 2 days prior to procedures with high bleeding risk. For patients with <30 mL/min, ribaroxaban should be ceased 2 days prior to procedures with low bleeding risk, and more than 2 days prior to procedures with high bleeding risk.

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Table 3. The recommendation of the Korean Heart Rhythm Society for patients with nonvalvular AF (continued)

8-4. For patients with CrCl ≥30mL/min, apixaban should be ceased 1 day prior to procedures with low bleeding risk, and 2 days prior to procedure with high bleeding risk. For patients with <30 mL/min, apixaban should be ceased 2 days prior to procedures with low bleeding risk, and more than 2 days prior to procedures with high bleeding risk.
9. Anticoagulation therapy for conducting an elective cardioversion or radiofrequency catheter ablation
9-1. To conduct elective direct current cardioversion for patients with AF of ≥48 hours duration or unknown time of occurrence, anticoagulant therapy with warfarin (INR 2.0–3.0) is recommended for ≥3 weeks prior to and ≥4 weeks after cardioversion to reduce the risk of thromboembolism.
9-2. To conduct radiofrequency catheter ablation for patients with AF of ≥48 hours duration or unknown time of occurrence, anticoagulant therapy with warfarin (INR 2.0–3.0) is recommended for ≥3 weeks prior to and 2 months after cardioversion to reduce the risk of thromboembolism.
9-3. For the application of NOACs prior to or after elective cardioversion, supporting evidence is currently insufficient and limited.
10. For patients with atrial flutter, antithrombotic therapy is recommended according to the same criteria applied for AF.

AF: atrial fibrillation, NOACs: novel oral anticoagulants, INR: international normalized ratio, TIA: transient ischemic attack

renal dysfunction (CrCl <30 mL/min).

8. Anticoagulant therapy for patients scheduled for an invasive procedure or surgery with the possibility of bleeding complications.

8-1. For patients on warfarin therapy, INR should be measured within 24 hours before an invasive procedure or a surgery, and an INR of ≤1.5 is generally considered safe with regard to the risk of periprocedural or perioperative bleeding. Warfarin can be reintroduced 24 hours later when hemostasis is confirmed and the patient is under a stable condition.

8-2. For patients with CrCl ≥50 mL/min, dabigatran should be ceased 1 day prior to procedures with low bleeding risk, and 2–3 days for high bleeding risk procedures. For patients with CrCl 30–49 mL/min, dabigatran should be ceased 2 days prior to procedures with low bleeding risk, and 3–4 days for high bleeding risk procedures.

8-3. For patients with CrCl ≥30 mL/min, rivaroxaban should be ceased 1 day prior to procedures with low bleeding risk, and 2 days prior to procedures with high bleeding risk. For patients with <30 mL/min, ribaroxaban should be ceased 2 days prior to procedures with low bleeding risk, and more than 2 days prior to procedures with high bleeding risk.

8-4. For patients with CrCl ≥30 mL/min, apixaban should be ceased 1 day prior to procedures with low bleeding risk, and 2 days prior to procedures with high bleeding risk. For patients with <30 mL/min, apixaban should be ceased 2 days prior to procedures with low bleeding risk, and more than 2 days prior to procedures with high bleeding risk.

During the administration of warfarin, bridge therapy can be considered for patients with high risk of thromboembolism. However, bridge therapy is not required with NOACs. Caution should be taken with NOACs, because there is no appropriate antagonist.

9. Anticoagulation therapy for conducting an elective cardioversion or radiofrequency catheter ablation

9-1. To conduct elective direct current cardioversion for patients with AF of ≥48 hours duration or unknown time of occurrence, anticoagulant therapy with warfarin (INR 2.0–3.0) is recommended for ≥3 weeks prior to and ≥4 weeks after cardioversion to reduce the risk of thromboembolism.

9-2. To conduct radiofrequency catheter ablation for patients with AF of ≥48 hours duration or unknown time of occurrence, anticoagulant therapy with warfarin (INR 2.0–3.0) is recommended for ≥3 weeks prior to and 2 months after cardioversion to reduce the risk of thromboembolism.

9-3. For the application of NOACs prior to or after elective cardioversion, supporting evidence is insufficient and limited.

In the subgroup analysis of the RE-LY trial with dabigatran, the incidence of thromboembolism did not increase in the first 30 days after defibrillation, compared to the incidence with warfarin. Currently, several studies investigating this issue are being conducted with NOACs, and the recommendation may be amended according to the study results.

10. For patients with atrial flutter, antithrombotic therapy is recommended according to the same criteria applied for AF.

The Characteristics in Stroke and Bleeding Complications When Treating with Warfarin or Novel Oral Anticoagulants in Asian Population: Ethnic Difference

Dabigatran versus Warfarin: Effects on Ischemic and Hemorrhagic Strokes and Bleeding in Asians and Non-Asians with Atrial Fibrillation[23]

A post hoc analysis was conducted with 2782 subjects (15%) from 10 Asian countries and 15331 subjects from 34 other countries, for a total study population of 18113 subjects in the RE-LY clinical trial, to compare the incidence of cerebral hemorrhage and severe bleeding according to dabigatran or warfarin therapy. In the Asian population, the incidence of cerebral hemorrhage was significantly

lower in both the dabigatran 110 mg (D110) and 150 mg (D150) groups than in the warfarin group (D110 versus warfarin HR, 0.15; 95% CI, 0.03–0.66 and D150 versus warfarin HR, 0.22; 95% CI, 0.06–0.77). Severe bleeding was also lower in both D110 and D150 groups compared to the warfarin group (D110 2.22% per year, D150 2.17% per year, and warfarin 3.82% per year). In the non-Asian population, there was no difference in the incidence of cerebral hemorrhage or severe bleeding.

Apixaban versus Warfarin: subgroup analysis on ARISTOTLE trial[7]

There is no report published so far analyzing the incidence of bleeding complication in the Asian population according to the use of apixaban or warfarin. But from the results of subgroup analysis in the ARISTOTLE trial, the incidence of severe bleeding in the Asian population was lower in the apixaban group than in the warfarin group.

Rivaroxaban for stroke prevention in East Asian patients from the ROCKET atrial fibrillation trial[24]

A total of 932 (6.5%) ROCKET AF participants resided in East Asia. Despite higher absolute event rates for efficacy and safety outcomes in East Asians, the relative efficacy of rivaroxaban versus warfarin with respect to the primary efficacy end point (stroke/systemic embolism) was consistent among East Asians and non-East Asians (interaction p=0.666). Relative event rates for major or nonmajor clinically relevant bleeding in patients treated with rivaroxaban and warfarin were consistent among East Asians and non-East Asians (interaction p=0.867). Observed relative efficacy and safety of rivaroxaban versus warfarin were similar in patients within and outside East Asia.

Nonwhite patients receiving warfarin had a significantly higher risk of ICH compared with whites, presenting a HR of 2.05 for blacks, 2.06 for Hispanics, and 4.1 for Asians. There was no difference in the incidence of ICH among racial groups not receiving warfarin.[25] Because the prevalence of hemorrhagic stroke is about 2.4 times higher in Asians than in other ethnic groups, the optimal INR rage in

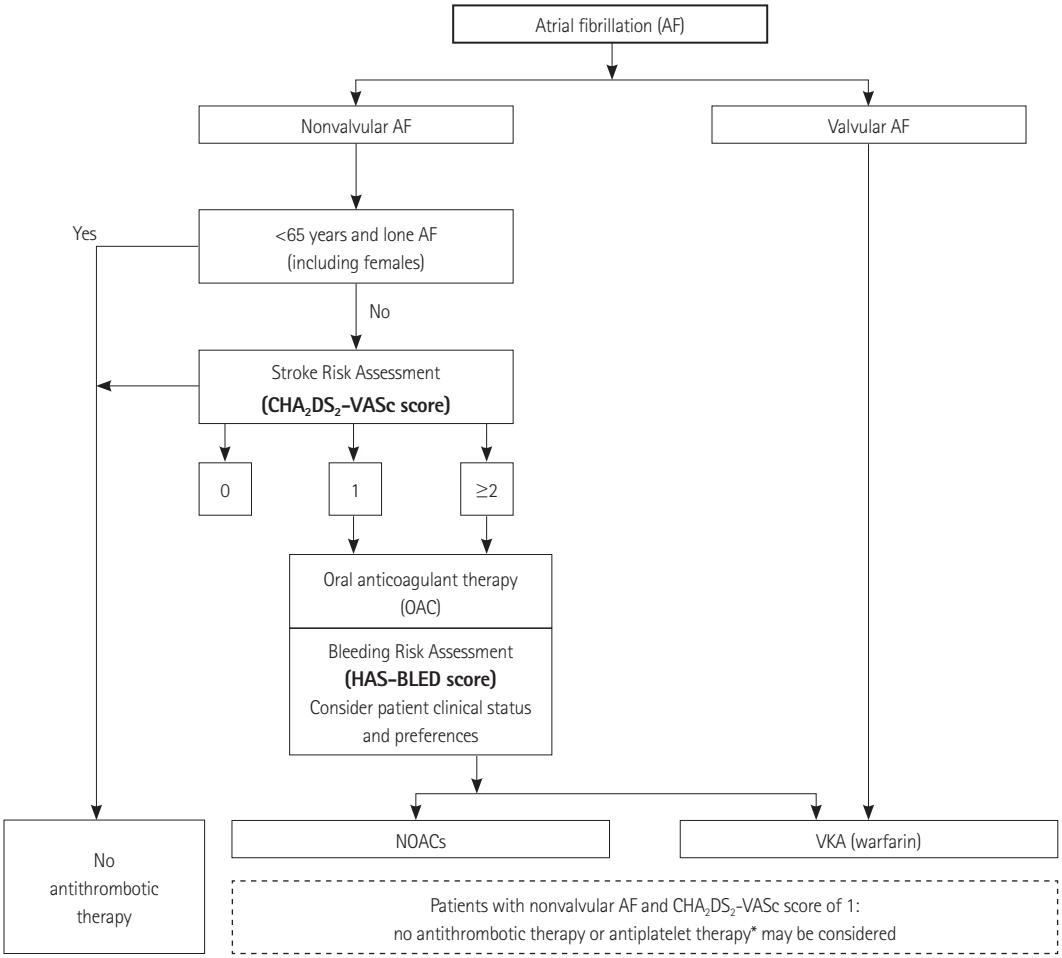

Fig. 1. The algorithm of antithrombotic therapy for patients with nonvalvular atrial fibrillation. *Aspirin, clopidogrel or both. Solid-line box: recommended option, dotted-line box: alternative option. NOACs: new oral anticoagulants, VKA: vitamin K antagonist.

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Asians was recommended as INR 1.6–2.6 for patients over 70 years in the APHRS 2013 guideline. The recently published meta-analysis data for all four NOACs, using data collected during the pivotal phase 3 clinical trials for stroke prevention and bleeding complication, presented a favorable risk-benefit profile with significant reduction in stroke, ICH, and mortality, with similar major bleeding as for warfarin.[16] Hence, with respect to ICH (including hemorrhagic stroke), NOACs can be very beneficial for Asian patients with nonvalvular AF, although additional supporting study results are required.

Conclusion

Antithrombotic therapy plays a very important role in preventing stroke and systemic thromboembolism in patients with nonvavular AF. However, the clinical characteristics of each patient should be carefully considered to maximize the preventative effect and minimize bleeding complications from the drug. The CHA_2DS_2-VASc score is recommended over the $CHADS_2$ score for assessment of stroke risk. To quantify bleeding risk, the HAS-BLED score is recommended. For patients with nonvalvualr AF and a CHA_2DS_2-VASc score of 0, antithrombotic therapy is not recommended. OAC therapy is recommended when the CHA_2DS_2-VASc score is 2 or greater. NOACs should be considered rather than warfarin if there is a possibility of bleeding complications and based upon the results of past studies. For patients with nonvalvualr AF and a CHA_2DS_2-VASc score of 1, OAC therapy is preferred, but no antithrombotic therapy or treatment with antiplatelet agents can be also considered (Fig. 1).

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